Chemotherapeutic Drugs in Pregnancy

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Most reproductive-aged women who have cancer are capable of ovulating and, therefore, able to conceive at any time. When pregnancy is diagnosed, chemotherapy may be continued or begun and should not be unnecessarily withheld. In general, systemic therapy for cancer in pregnancy must be individualized and may be different if the patient is diagnosed during the first versus the second or third trimesters. Chemotherapy during the first trimester may cause more severe fetal effects, and in cases where a malignancy that requires chemotherapy is diagnosed during the first trimester, termination of pregnancy is a consideration.

For women who do not request pregnancy termination, the choice of drugs must take into account the fetus and may direct therapy to non-standard regimens (for example, single versus combination therapy). For malignancies diagnosed in the second trimester, consideration for the fetus with respect to drug effects should be given, but in cases of a maternal cancer that responds to chemotherapy, it is unwise to delay treatment until after delivery. Termination of pregnancy is also a possibility, but the effects of the medications on the fetus will potentially be less than in the first trimester.

The likely adverse effects on the fetus have prompted practitioners to consider delaying chemotherapy until the postpartum period for cancers diagnosed in the third trimester. Although it is not prudent to put off definitive treatment for more than a few weeks, it may be possible to effect an early delivery (after steroid therapy to improve fetal lung function and to limit intracranial bleeds) and proceed with chemotherapy in the postpartum period. The University of New

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Mexico, has offered early delivery for gestations that are past 34 weeks in cases of maternal cancer. At this gestational age, the long-term outcome of a baby approaches that of a term infant. The mother can then receive definitive chemotherapy postpartum without exposing her fetus to potential harm.

**Fetal risks**

Physiologic changes of pregnancy must be considered when prescribing chemotherapy. Drugs are easily absorbed, and the serum concentration of albumin for drug binding is lower than when a woman is not pregnant. Pharmacokinetic changes during pregnancy include a higher volume of distribution, lower maximum plasma concentration, lower steady serum state concentration, lower plasma half-life, and higher clearance rate. The small spatial configuration and the high lipid solubility of most chemotherapy facilitate easy transfer of an unbound drug or its metabolite across the placenta or into the breast milk. Virtually all drugs cross the placenta, and therefore, unbound concentrations of the drug are similar or higher in the fetal serum and amniotic fluid than in the maternal serum.

Fetal exposure may be divided into three periods: (1) ovum, from fertilization to implantation; (2) embryo, from the second through the eighth week; and (3) fetus, from the eighth completed week until term. Experience with first trimester exposure for any drug is often too limited in humans to be considered absolutely safe. The embryo period encompasses the most critical time with respect to physical malformations, because it involves organogenesis. The background risks of major defects are about 3% at birth and about 4.5% by 5 years of age.

Despite being infrequent, detrimental effects may occur when certain drugs are taken beyond organogenesis. Few drugs, however, have been implicated in restricting fetal growth or in grossly reducing specific organ size. Of particular importance when prescribing chemotherapy, are the exact dose of the agent and the genetic sensitivity of the mother and fetus. Results of retrospective and uncontrolled studies and individual case reports may be misleading regarding the risk of exposure to specific chemotherapy during pregnancy. Differentiating between effects of a specific pharmacologic agent and effects from an illness can be difficult. There is virtually no information about long-term effects, such as learning or behavior problems (functional teratogenesis), that may result from the chronic prenatal exposure to chemotherapy.

Drugs prescribed during pregnancy have been assigned a risk factor (A, B, C, D, or X) according to definitions provided by the U.S. Food and Drug Administration. Chemotherapeutic agents generally fall into the C or D categories. Drugs in the C category are those for which studies in animals have revealed adverse effects on the fetus (embryocidal, teratogenic, or other) and controlled studies in women or studies in women and animals are not available. Drugs in the D category are those for which there is positive evidence of human fetal risk, but
the benefit justifies the potential risk to the fetus. Most human data about chemotherapy during pregnancy involve small series or case reports. Such information may either be biased or merely reflect the patient’s background risk for birth defects. Case reports of malformed infants after prenatal exposure to a certain drug, may feature exposures to other agents and a lack of uniformity of abnormalities, which makes their association with a single causative agent unlikely.

Counseling for pregnancy and breastfeeding

The long-term effect of chemotherapy on female and male reproductive function has been reported for select agents. Menstrual function in most women in regular and premature menopause is very uncommon. Menstrual difficulties are usually not serious or persistent. Problem-free conceptions or, less commonly, initial infertility followed by conception is the norm. We are unaware of any safe minimum time after stopping the drug and conceiving. In addition, spermatogenesis is not impaired long-term. Any infertility requires an assessment of the male factor that includes a sperm count and ejaculate volume.

Treating cancer during pregnancy requires compromises and makes the management of pregnant women who have cancer one of the most challenging areas in all of medicine. This dilemma must take into account the health and welfare of the mother and the fetus, which are at odds when it comes to the use of chemotherapy. Combination therapy is optimal because multiple partially effective drugs used together interrupt a broader range of proliferative pathways that may be pivotal to the growth of individual cells or cell clones. The use of more than one drug is, however, likely to have a greater negative impact on the pregnancy.

A lack of comparability of the dose and the route of administration can also limit interpretation. For example, the short-term administration of a drug given intravenously makes it difficult to relate risk when the same medication is taken orally in a lower dose for a longer period. Because a control population is not possible, it is also difficult to separate any hazard from the medication with that of an underlying disease. Symptoms of pregnancy such as nausea, fatigue, and gastrointestinal disturbance may mimic side effects or toxic reactions to chemotherapy.

Counseling about any harmful risk to the fetus should be performed in a sympathetic, supportive, and informative manner. A detailed targeted ultrasound examination is often used to accurately date the pregnancy and to screen for fetal structural defects. The authors are unaware of any risk of chromosomal abnormalities with chemotherapy before or after conception. For this reason, prenatal genetic testing by first trimester screening, serologic testing, chorionic villus sampling, and amniocentesis, are not recommended. Sources of information regarding potential teratogens include computerized databases online and on diskette. Numerous teratogen information services are available throughout the United States to serve specific geographic areas. Additional sources to which the reader

None of the chemotherapeutic agents described here has been proven safe for breastfeeding, and manufacturers recommend breastfeeding be avoided. Contraindications or cautions to breastfeeding are unknown, theoretical, or founded on limited case reports. In general, most medications are excreted in breast milk (often less than 5% of weight adjusted maternal daily doses) leading to legitimate concerns regarding neonatal effects. The amount of drug present in the milk and consumed by the infant depends on the chemical properties of the drug and on the dose, frequency, and duration of exposure. Neonatal neutropenia, immune or bone marrow suppression, and reduced growth are particular concerns with exposure to any chemotherapy.

This article reviews specific effects of commonly used agents by category. For each drug, the literature has been reviewed to provide information on the indication(s), mechanism of action, tissue distribution, maternal and fetal side effects, and breastfeeding information. Information provided in a previous review [1] has been updated and expanded.

**Alkylating agents**

Cyclophosphamide (Cytoxin, CTX, CPM, Neosar) is a commonly used agent indicated for breast cancer, non-Hodgkins lymphoma, chronic lymphocytic leukemia, ovarian cancer, bone and soft tissue sarcoma, rhabdomyosarcoma, neuroblastoma, and Wilm’s tumor. Cyclophosphamide is also an immunosuppressant and may be indicated for other complications of pregnancy in addition to cancer. The mechanism of action depends upon the fact that cyclophosphamide is activated by the liver cytochrome P450 microsomal system to produce cytotoxic metabolites phosphoramid mustard and acrolein. The metabolites form cross-links with DNA which results in inhibition of DNA synthesis. This agent is active in all stages of the cell cycle. Cyclophosphamide is distributed throughout the body including the brain, cerebrospinal fluid, milk, saliva, and, presumably the amniotic fluid. The drug is given either orally or intravenously, and care providers who administer cyclophosphamide have been reported to absorb measurable quantities of the agent through the skin or air as an aerosol. Women who administer chemotherapy should be aware of this and avoid contact with such drugs during pregnancy [2]. The major maternal side effect is myelosuppression, which is dose-limiting. Normal as well as malformed fetuses have been reported from exposures during the first trimester [3]. The defects reported include ocular anomalies, malformations, missing digits and nail abnormalities, coronary artery defects, umbilical hernia, hemangioma, imperforate anus, rectovaginal fistula, cleft palate, microcephaly, growth restriction, and developmental delays [3]. Second and third trimester exposures are not associated with malformations, but
are linked to growth restriction, microcephaly, and possibly, neonatal pancytopenia [4]. As with alkylating agents in general, the use of cyclophosphamide is also associated with subsequent menstrual difficulties and premature ovarian failure, although a recent study suggests that successful post-therapy pregnancies are not uncommon [5].

Thiotepa (Triethylenethiophosphoramide, TSPA, Thioplex, Girostan, Tespamin, Thiotef) is indicated for the treatment of breast cancer, ovarian cancer, superficial transitional cell cancer of the bladder, and Hodgkin’s and non-Hodgkin’s lymphoma. Thiotepa is an ethylenimine analog that is chemically related to nitrogen mustard, which alkylates the N-7 position of guanine. This damages DNA and inhibits DNA, RNA, and protein synthesis. The drug is active in all phases of the cell cycle and is widely distributed throughout the body including, presumably, the amniotic fluid. Intravenous infusion is required. Little is known about the fetal effects in humans, but thiotepa has been used during the second and third trimesters without apparent harm in one pregnancy [6]. When rats were given high doses of this agent, many of the fetuses died in utero. Multiple malformations are common in surviving pups [7]. In mice, fetal lethality is also a substantial problem, and pups that do not die initially demonstrate a high incidence of skeletal abnormalities when exposed to a maternal dose of 5 mg/kg [8].

Chlorambucil (Leukeran) is indicated for the treatment of chronic lymphocytic leukemia and low-grade, non-Hodgkin’s lymphoma. Chlorambucil is an analog of nitrogen mustard that cross-links with DNA and inhibits DNA synthesis and function. It is active in all phases of the cell cycle. Chromosomal damage has been documented in human cells following chlorambucil therapy [9]. The drug is given orally, but distribution has not been adequately studied. Myelosuppression is dose-limiting and nadirs at 25–30 days after therapy. As with other alkylating agents, gonadal damage after exposure is a consideration. This raises a concern for premature ovarian failure in women and oligospermia in men [10,11], although the agent has been given to patients with recovery of gonadal function and successful pregnancies thereafter [12,13]. Normal pregnancies as well as pregnancies complicated by fetal malformations have been reported after chlorambucil use [14]. Potential effects on the fetus include unilateral agenesis of the left kidney and ureter in male fetuses following first trimester exposure as well as cardiac defects [15,16]. The most consistent finding is renal agenesis in both humans and animals [15–17]; however, the magnitude of the risk in exposed fetuses is not known at this time.

Melphalan (Alkeran, phenylalanine mustard, L-PAM) has been used to treat multiple myeloma, breast cancer, and ovarian cancer. Melphalan is an analog of nitrogen mustard. It forms interstrand and intrastrand cross-links with DNA which results in inhibition of DNA synthesis and function. The drug is active in all phases of the cell cycle and is widely distributed throughout the body including, presumably, the amniotic fluid. It can be given orally or intravenously. The principal maternal toxicity is myelosuppression. Ovarian failure and amenorrhea have been reported in women taking melphalan [18,19]. No reports
have appeared that link melphalan with congenital defects, although it is possible that this drug has similar effects to other alkylating agents in pregnancy (see cyclophosphamide).

Busulfan (Myleran, Busulfex) is indicated principally for chronic myelogenous leukemia. This is a methanesulfonate-like bifunctional alkylating agent that interacts with thiol groups and causes nucleic acid and protein cross-links. Busulfan is active in all phases of the cell cycle. The drug distributes rapidly in all tissues and crosses into the amniotic fluid and the blood brain barrier. It is given orally or intravenously. Maternal toxicity includes myelosuppression, which is dose-limiting. Rarely, a severe and life threatening form of pulmonary fibrosis results, which may occur 1 to 10 years after therapy. Six of 22 fetuses exposed to busulfan in the first trimester demonstrated malformations including liver and spleen abnormalities, pyloric stenosis, cleft palate, microphthalmia, cytomegaly, hypoplasia of the ovaries and the thyroid, growth restriction, hydronephrosis and absent kidney and ureter [20–22].

Cisplatin (Cis-diamminedichloroplatinum, CDDP, Platinol) is indicated for ovarian cancer, bladder cancer, head and neck cancer, cancer of the esophagus, small cell and non-small cell lung cancer, non-Hodgkin’s lymphoma, and choriocarcinoma. Cisplatin covalently binds to DNA preferentially at the N-7 position of guanine and adenine causing cross-links. It also binds to nuclear and cytoplasmic proteins and causes cytotoxic effects. It is widely distributed in all tissues but the highest concentrations occur in the liver and kidneys. The drug is given intravenously or directly into the peritoneal cavity (not absorbed orally). Maternal side effects include nephrotoxicity and neurotoxicity, which are dose-limiting. Myelosuppression is also a factor. Limited use has been reported in pregnancy [23]. There are recent reports of normal neonates born after in utero exposure to a combination of paclitaxel and platinum for ovarian cancer during pregnancy [24,25]. The breastfeeding advice is conflicting. Some references suggest that breastfeeding is possible with caution [26]; however, other references state that breastfeeding should be avoided based upon a report of excretion into breast milk [27].

Carboplatin (Paraplatin, CBDCA) is indicated for ovarian cancer, germ cell tumors, head and neck cancer, small cell and non-small cell lung cancer, bladder cancer, relapsed and refractory acute leukemia, and endometrial cancer. Carboplatin forms DNA cross links preferentially by binding to the N-7 position of guanine and adenine. It is cell cycle non-specific and is widely distributed throughout all body tissues, including presumably, the amniotic fluid. This agent is given intravenously and is not absorbed orally. Maternal myelosuppression is significant and dose-limiting; nephrotoxicity and neurotoxicity are less than with cisplatin. The pregnancy risk category is D; information about fetal effects is limited but likely to be similar to cisplatin. The breastfeeding risks are unknown.

Dacarbazine (DIC, DTIC-Dome, Imidazole carboxamide) is indicated for the treatment of melanoma, Hodgkin’s disease, soft tissue sarcomas, and neuroblastoma. Dacarbazine is a non-classical alkylating agent that prevents the biosynthesis of purines. It methylates nucleic acids and inhibits DNA, RNA, and
protein synthesis. This agent is distributed throughout the body and fluid spaces. It is loosely bound to plasma proteins. Dacarbazine is given by the intravenous route, and maternal myelosuppression is dose-limiting. Fetal rats exposed to doses ranging from 200 mg to 600 mg demonstrated renal pyelectasis [28]. However, it has been reported that use of dacarbazine in the treatment of metastatic melanoma during the second and third trimester in combination with other medications (carmustine, tamoxifen, and cisplatin) apparently caused no ill-effects. In this case, the baby was delivered prematurely at 30 weeks, but was otherwise healthy [29].

Antibiotics

Dactinomycin-D (Actinomycin-D, Act-D, Cosmegen) is indicated for Wilm’s tumor, rhabdomyosarcoma, germ cell tumors, gestational trophoblastic disease, and Ewing’s sarcoma. Dactinomycin-D is a product of Streptomyces species that is composed of a tricyclic phenoxazone chromophore linked to two cyclic polypeptides. This agent binds to guanine-cytidine base pairs and inhibits DNA synthesis and function. It also causes the accumulation of intracellular oxygen-free radicals that further damage DNA. This drug must be given intravenously and is not absorbed orally. Dactinomycin-D concentrates in nucleated blood cells and is highly protein-bound. Maternal myelosuppression is dose-limiting. Reports of the use of dactinomycin-D in the second and third trimesters have revealed apparently normal neonates [10,30–33].

Bleomycin (Blenoxane) is indicated for Hodgkin’s disease and non-Hodgkin’s lymphoma, germ cell tumors, head and neck cancer, and squamous cell carcinomas of the skin, cervix, and vulva. This drug is a small peptide antibiotic that binds iron to create activated oxygen-free radicals causing breaks in DNA. Bleomycin is given intravenously or directly into the pleural space (not absorbed orally); it is found in the intra and extracellular fluid, where less than 10% is bound to proteins. The major maternal toxicity is pneumonitis, which is dose-limiting. While chromosomal aberrations in human bone marrow cells have been reported [34], no congenital defects have been linked to the use of bleomycin in pregnancy. Second and third trimester exposures in combination with other agents have resulted in the delivery of normal babies [27,31,35,36].

Antimetabolites

Methotrexate (MTX, Amethopterin) is indicated for the treatment of breast cancer, head and neck cancer, osteogenic sarcoma, acute lymphocytic leukemia, non-Hodgkin’s lymphoma, meningeal leukemia and meningitis, bladder cancer, colorectal cancer, and gestational trophoblastic disease. Methotrexate is a classic folic acid analog/antagonist, and its action is specific for the S-phase of the cell cycle. The drug enters the cell through the folate transport system and inhibits the
enzyme dihydrofolate reductase, thus depleting the level of reduced folates necessary for critical cell functions. Methotrexate also inhibits de novo thymidylate and purine synthesis. Upon treatment, it is widely distributed throughout the body including fluid spaces such as the amniotic fluid. The drug is given by the intravenous, intramuscular, or oral routes. Maternal myelosuppression is dose-limiting. Also, acute renal failure caused by intratubular precipitation of methotrexate or its metabolites can occur. In the first trimester, methotrexate is clearly associated with teratogenicity. Malformations include severe cephalic and skull abnormalities with the absence of sutures, absence of the frontal bone, hypertelorism, a depressed or widened nasal bridge, hypoplasia of the mandible, heart defects such as dextroposition, and other conditions including the absence of digits. The attack rate appears to be relatively high; nearly one-third of exposed fetuses demonstrate malformations [37–39]. In addition, late effects of methotrexate on brain development are possible and should be studied further [40].

5-Fluorouracil (5FU, Efudex) is indicated for colorectal cancer, breast cancer, gastrointestinal malignancies, head and neck cancer, skin cancer, hepatoma, and ovarian cancer. This agent is a pyrimidine analog specific for the S-phase of the cell cycle. Metabolic forms are incorporated into DNA and RNA to disrupt cell function. Given intravenously, it is widely distributed in tissues and fluid spaces, including, presumably, the amniotic fluid. Maternal myelosuppression, mucositis, or diarrhea may each be dose-limiting. Hand-foot syndrome, manifested by tingling, skin and nail changes, pain or numbness may also be dose-limiting. Normal as well as malformed fetuses have resulted from exposure to 5-fluorouracil. In one report, first trimester treatment was associated with multiple anomalies including radial dysplasia, absent digits, and hypoplasias of thoracic and abdominal organs such as the lungs, aorta, esophagus, duodenum, and ureters, among other defects [41].

**Nucleoside analogues**

Cytarabine (Cytosine arabinoside, Ara-C, CytoSar-U) is indicated for acute myelogenous leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, and leptomeningeal carcinomatosis. This agent is a deoxycytidine analog synthesized by the sponge *Cryptothecethya crypta*. Its activity is specific for the S-phase of the cell cycle where the drug incorporates as a metabolite, ara-C triphosphate, into DNA. This results in the termination of DNA chain synthesis. Intravenous administration results in wide tissue distribution throughout the body including fluid spaces such as the amniotic cavity. The drug is inactive orally. Myelosuppression is dose-limiting for the patient, and the pregnancy risk category is D. First trimester exposures have been associated with otic anomalies and auditory canal atresia, lobster claw hand and other digital anomalies, as well as lower limb defects [42,43]. In addition to the potential for the usual growth restriction in fetuses exposed later in pregnancy, reports of fetal death in utero
associated with cytarabine or combinations including cytarabine have appeared in the literature [44]. Breastfeeding data are not available.

Gemcitabine (Gemzar) is indicated for cancer of the pancreas, bladder cancer, non-small cell lung cancer, and soft tissue sarcoma. This drug is a fluorine-substituted deoxycytidine analog that inhibits the cell cycle at the S-phase. Drug exposure results in the incorporation of a metabolic triphosphate nucleotide product, dFdCTP, into DNA that causes chain termination and stops DNA synthesis and function. Gemcitabine is administered by the intravenous route and is not extensively distributed in the body; however, it does cross the blood-brain barrier and may cross the placenta. Maternal myelosuppression is dose-limiting. No information on humans is available at this time; however, gemcitabine is teratogenic in mice and rabbits.

**Topoisomerase I inhibitors**

Topotecan (Hycamtin) is indicated for ovarian cancer, small cell lung cancer, and acute myelogenous leukemia. Topotecan is an alkaloid derivative from the *Camptotheca acuminata* tree that inhibits topoisomerase I function. Topotecan binds to and stabilizes the topoisomerase I-DNA complex and prevents the release of DNA after it has been cleaved by topoisomerase I. The complex collides with the advancing replication fork and stops DNA synthesis. This agent is widely distributed in body tissues and is given intravenously. The major maternal toxicity is myelosuppression (dose-limiting) with the neutropenic nadir occurring at 7 – 10 days. No information from humans is available at this time; however, topotecan is teratogenic in animals in dosages that approximate recommended human regimens.

Irinotecan (Camptosar, CPT-II) is indicated for colorectal cancer and non-small cell lung cancer. Irinotecan is a synthetic derivative of camptothecin, an alkaloid derivative of the *Camptotheca acuminata* tree. The active metabolite of irinotecan, SN-38, stabilizes the topoisomerase I-DNA complex and prevents normal DNA synthesis and function. The drug is cell cycle non-specific. This agent is widely distributed throughout the body and is administered intravenously. Myelosuppression is dose-limiting. No studies reporting its use in pregnancy or breastfeeding have appeared.

**Topoisomerase II inhibitors**

Etoposide (VePesid, VP-16) is indicated for germ cell tumors, small cell lung cancer, non-small cell lung cancer, non-Hodgkin’s lymphoma, and gastric cancer. Etoposide is an alkaloid extracted from the *Podophyllum peltatum* mandrake plant that inhibits topoisomerase II by stabilizing the topoisomerase II-DNA complex and preventing DNA unwinding. Etoposide is active during the S- and G2-phases of the cell cycle and is rapidly distributed into all body fluids and
tissues when administered either by the intravenous or the oral route. Decreased albumin, as may occur during pregnancy, has the potential to result in elevated free drug levels and toxicity. For the mother, myelosuppression is dose limiting, and etoposide may prolong the prothombin time and the INR. Use of etoposide in pregnancy has not resulted in reported fetal malformations; however, intrauterine growth restriction and pancytopenia in neonates have been reported [45,46]. One child whose mother received etoposide developed ventriculomegaly during the pregnancy and subsequently developed cerebral atrophy [47]; however, most newborns who have been exposed during the second and third trimesters show no abnormalities at two years of development.

Doxorubicin (Adriamycin, Adria, Hydroxydaunorubicin, DOX, Rubex) is indicated for breast cancer, Hodgkin’s and non-Hodgkin’s lymphoma, soft tissue sarcoma, ovarian cancer, non-small cell and small cell lung cancer, bladder cancer, thyroid cancer, hepatoma, gastric cancer, Wilm’s tumor, neuroblastoma, and acute lymphoblastic leukemia. Doxorubicin is an anthracycline antibiotic isolated from Streptomyces species that intercalates into DNA, which inhibits DNA synthesis. The drug also inhibits transcription, by inhibiting DNA-dependent RNA polymerase, and the function of topoisomerase II. This agent is widely distributed when given by the intravenous route; about 75% of the drug and metabolites are bound to plasma proteins. Myelosuppression is dose limiting; however, cardiotoxicity, both acute and chronic, are well-described. The acute form presents with arrhythmias and conduction abnormalities and is not dose-related; however, chronic cardiotoxicity is dose-related and results in dilated cardiomyopathy. First trimester exposures, sometimes in combination with other drugs or radiation, have resulted in normal and abnormal neonates. Imperforate anus and rectovaginal fistula have been described as well as microcephaly [48]. The effects of doxorubicin on the hearts of exposed fetuses and neonates are under evaluation [49], but no definitive information is available. Doxorubicin is excreted in breast milk [50].

Daunorubicin (Daunomycin, DNR, Cerubidine, Rubidomycin) is indicated for acute myelogenous leukemia and acute lymphoblastic leukemia. This drug intercalates into DNA and causes damage by forming a complex between DNA and topoisomerase II. Daunorubicin is widely distributed throughout the major organ systems and is highly lipid soluble. It is given intravenously. Myelosuppression is dose-limiting, and cardiotoxicity is usually transient, but can persist in a chronic form that leads to dilated cardiomyopathy. Fetal effects are presumed to be similar to doxorubicin.

**Vinca alkaloids**

Vincristine (Oncovin, VCR) has been used to treat acute lymphoblastic leukemia, Hodgkin’s and non-Hodgkin’s lymphoma, multiple myeloma, rhabdomyosarcoma, neuroblastoma, Ewing’s sarcoma, Wilm’s tumor, chronic leukemias, thyroid cancer, brain tumors, and choriocarcinoma. Vincristine is a vinca
alkaloid antimicrotubule agent derived from the periwinkle plant *Catharanthus roseus*. Vincristine inhibits tubulin polymerization and disrupts mitosis; hence this drug is principally active during the M-phase of the cell cycle. This agent is rapidly distributed throughout the body but with relatively poor penetration of the blood-brain barrier; it is given intravenously. Neurotoxicity is dose limiting, and the clinical manifestations include peripheral neuropathy, autonomic nervous system dysfunction, cranial nerve palsies, seizures, cortical blindness, and coma. Various sporadic reports of vincristine use in pregnancy and associated fetal anomalies have appeared. These include the presence of an atrial septal defect, renal hypoplasia, and pancytopenia [4,51,52].

Vinblastine (Velban) has been used to treat Hodgkin’s and non-Hodgkin’s lymphoma, breast cancer, Kaposi’s sarcoma, and renal cell carcinoma. Vinblastine is a plant alkaloid from the periwinkle plant *C. roseus*. It inhibits tubulin polymerization and disrupts microtubules during the M-phase of the cell cycle. It is given intravenously and is widely distributed to most body tissues, but with poor penetration of the blood-brain barrier. Myelosuppression is dose-limiting for the mother, and neurotoxicity is less than with vincristine. Exposure during the first trimester has been associated with normal outcomes [53]; however, a review of cases of vinblastine therapy during pregnancy identified three human cases of suspected teratogenicity. One case was a spontaneous abortion, another resulted in a child with hydrocephalus (first trimester exposure), and another case resulted in the birth of an infant with cleft lip/palate after exposure to a multi-drug regimen including vinblastine [19].

Vinorelbine (Navelbine) may be indicated to treat non-small cell lung cancer, breast cancer, ovarian cancer, and Hodgkin’s lymphoma. This agent is a semi-synthetic form of vinblastine with similar actions, which is widely distributed throughout the body and is 80% protein bound. It is given intravenously. Maternal myelosuppression is dose-limiting. Vinorelbine is known to be teratogenic in animals, but sparse data are available in humans.

**Taxanes**

Paclitaxel (Taxol) is indicated for the treatment of ovarian cancer, breast cancer, non-small cell and small cell lung cancer, head and neck cancer, esophageal cancer, prostate cancer, bladder cancer, endometrial cancer, and AIDS-related Kaposi’s sarcoma. Paclitaxel is isolated from the Pacific yew tree, *Taxus brevifolia*. The drug acts by binding to microtubules and enhancing polymerization. Mitosis is inhibited in the M-phase of the cell cycle. This agent is widely distributed throughout the body, including fluid spaces; however, paclitaxel has poor blood brain barrier penetration. It is given by the intravenous route. Myelosuppression is dose-limiting, and neurotoxicity is a consideration. Rare cases of fatal anaphylaxis have been reported. A few case reports of human fetal exposures have appeared in the literature. These include one patient who was treated from 16 weeks until delivery; the baby was reported to be normal at
15 months [24], and another patient who was treated from 27 weeks until delivery; the baby was a normal neonate when evaluated at 30 months of age [25]. Paclitaxel is highly lipophilic, and minimal kinetic information is available.

**Biologics and growth factor pathway blocking agents**

Trastuzumab (Herceptin) is one of a new class of anti-cancer therapies that block the epidermal growth factor receptor (EGFR) pathway. Specifically, trastuzumab blocks the HER-2/neu receptor, a member of the EGFR family. This agent has shown promise in the treatment of breast and lung cancer and is in trials for treatment of endometrial and ovarian cancer, among other sites. It has now gained approval from the Food and Drug Administration for the treatment of advanced breast cancer. Interestingly, the manufacturer has assigned a pregnancy risk category of B to trastuzumab based upon extensive trials in monkeys without apparent fetal harm. Placental transfer in monkeys was demonstrated. However, a case report of the use of trastuzumab in human pregnancy reveals an association with significantly decreased amniotic fluid, indicating an adverse effect on the fetal kidney [54]. In addition, mice in which the HER-2/neu gene has been deleted, die during embryogenesis because of heart defects or lack of proper cardiac development [55]. These reports indicate that biologics, as well as classic chemotherapy agents, have the potential to affect the fetus and should be used with caution for the treatment of cancer in pregnancy.

**References**


